

## REMARKS

An Office Action was mailed in the above-captioned application on April 8, 2003. In such Office Action claims 1-40 were pending. Claims 1-40 were rejected. This Amendment and Remarks document is submitted in response to said Office Action.

### The Rejection under 35 U.S.C. § 112, second paragraph

The Examiner has rejected Claims 1-40 under 35 U.S.C. § 112, second paragraph. The second paragraph of Section 112 requires that the claims set out and circumscribe a particular area which applicants regard as their invention with a *reasonable* degree of precision and particularity.

(a) The Examiner asserts that Claims 1, 9, 15, 19, 28, and 33 are confusing because the claimed methods appear to be redundant in that all of them lead to the preparation or design of the same product. The Examiner further asserts that in each claimed method the product is “defined” by modifying a nucleic acid via adding, deleting or substituting nucleotide residues wherein the residues may be chemically modified and/or chemically modifying the nucleic acid ligand such that none of the methods generates a product that is distinct from the product of any other method. Finally, the Examiner asserts that Claims 9, 15, 19, 28 and 33 in which the recited modifications are “based on” a previous recited determination, such as the three-dimensional structure of the nucleic acid ligand, the residues responsible for the target binding or the consensus sequence of multiple nucleic acid ligands, are indeterminate in that the modifications have no relationship to the “determination” on which they are putatively “based.”

Claim 9 step f); Claim 15, step b); and Claim 19, step g) have been amended to clarify that the determining comprises determining which nucleic acid residues in a nucleic acid ligand are necessary for maintaining the three-dimensional structure of the ligand, which residues interact with the target to facilitate the formation of ligand-target binding pairs, or both. Support for this amendment can be found at page 12, line 25 to page 13, line 2.

Claim 28, step g) has been amended to clarify that the adding nucleotide residues is adding random a sequence of nucleotide residues to the minimal consensus primary structure, and that the deleting or substituting nucleotide residues is deleting or substituting nucleotide

residues not conserved in the consensus primary structure. Support for this amendment can be found at page 30, lines 17-18, and at page 26 line 26, for example.

Claim 33, step g) has been amended to clarify that the addition, deletion or substitution of nucleotide residues is the addition, deletion or substitution of nucleotide residues of a consensus loop, or consensus bulge, or a consensus stem, including pairs of base-paired nucleotide residues in a consensus stem. Support for this amendment can be found, for example in section V., especially pages 36, and 39-40.

It is believed that the claims are not “redundant” in that the methods recite different method steps, which have now been further clarified by amendments described above, and that the methods would not necessarily result in products that are not distinct from each other. Regarding Claim 1, no amendment has been made to claim 1 under this section. It is unclear if the rejection of Claim 1 is based solely on its alleged redundancy with other claims, or for an additional reason. Clarification is requested.

(b) The Examiner asserts that claims 4, 12, 18, 22, 31 and 36 are confusing in appearing to be redundant for the reasons given above in (a) for the claims from which claims 4, 12, 18, 22, 31 and 36 depend. The Examiner further asserts that the “improved nucleic acid ligands” to which these claims are drawn lack distinguishing characteristics. For the reasons given above in a), it is believed that these products are not “redundant,” and that the products are distinct from each other given the differing methods used to obtain them.

(c) The Examiner asserts that in Claims 1, 9, 28, and 33 the final “determining” step lacks antecedent basis in previous steps in that the “enhanced target function altering activity” should be compared not with the ligand *per se* but with its activity prior to improvement. As suggested by the Examiner, Claim 1, step g) has been amended to recite “the target function altering activity of the nucleic acid ligand of step e)”. Claims 9, 28, and 33 have been similarly amended.

(d) The Examiner asserts that in Claim 33, step e) “target modulatory activity” is *non sequitur* to “target function altering activity” elsewhere in the claim. “Target modulatory activity” has been amended to recite “target function altering activity.”

(e) The Examiner asserts that Claim 39 is incomplete in omitting an essential step, such omission amounting to a gap between the steps, and that the omitted step is determining the cell membrane permeability of the nucleic acid ligand identified in step d). Claim 39 has been

amended to add new step e), which recites "determining the cell membrane permeability of said nucleic acid ligand". Consequently steps e), f) and g) have been relabeled as steps f), g) and h).

(f) The Examiner asserts that in Claim 39 the final "determining" step lacks antecedent basis in previous steps and that the "enhanced target function altering activity" should be compared not with the ligand *per se* but with its activity prior to improvement. It is believed that the Examiner meant to refer to the cell membrane permeability rather than "enhanced target function altering activity." The last step of claim 39 has been amended to refer to the membrane permeability of the nucleic acid ligand of step e).

(g) The Examiner asserts that Claim 39 is confusing due to the extraneous word "said" in step e). The word "said" has been deleted from Claim 39.

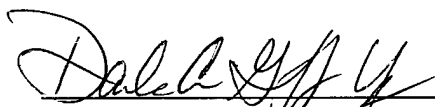
Additionally, Claim 6 has been amended to correct the spelling of "claim" It is believed that the claim amendments are sufficient to overcome the rejection over 35 U.S.C. § 112, second paragraph. Reconsideration is respectfully requested.

#### Closing Remarks

Applicant believes that the pending claims are in condition for allowance. If it would be helpful to obtain favorable consideration of this case, the Examiner is encouraged to call and discuss this case with the undersigned.

This constitutes a request for any needed extension of time and an authorization to charge all fees therefore to deposit account No. 19-5117, if not otherwise specifically requested. The undersigned hereby authorizes the charge of any fees created by the filing of this document or any deficiency of fees submitted herewith to be charged to deposit account No. 19-5117.

Respectfully submitted,



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